



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

May 25, 2000

**MEMORANDUM**

**SUBJECT:** **Propargite**; P.C. Code 097601. The REVISED HED Toxicology Chapter for the Risk Assessment for the Reregistration Eligibility Decision Document (RED), Case # 0243. DP Barcode: D266213

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Attached is the revised Toxicology Chapter for propargite for purposes of issuing a Reregistration Eligibility Decision (RED) Document. This document has been amended and contains error corrections and comments as requested by Uniroyal Chemical (letter and attachments, W. Cummings, 4/27/00).

## HAZARD CHARACTERIZATION

### Hazard Profile

Propargite is an organosulfur miticide used for the control of agricultural pests. The toxicological data base for propargite is complete (See Table 1) and will support reregistration eligibility.

Propargite is considered **corrosive** and has been placed in Category I **for both eye and dermal irritation** in rabbits. There have also been documented reports of dermal and eye irritation developing in workers exposed to Propargite in the field. Evidence for its dermal sensitization potential have been noted; a study that provides conclusive results has not been possible due to the irritating properties of this chemical. However, the acute toxicity is low (Category III) via the oral (rat: LD<sub>50</sub> = 2639 mg/kg for males, 2947 mg/kg for females) and dermal (rabbit: LD<sub>50</sub> > 2000 mg/kg) routes of exposure.

The available studies demonstrate no increased sensitivity of rats or rabbits to in utero and/or postnatal exposure to Propargite. In the rat developmental study (MRID 41346501), no developmental toxicity was noted at the highest dose tested and maternal toxicity was shown to occur at a dose lower than that for fetuses [for rat, the maternal NOAEL is 25 mg/kg/day and the developmental NOAEL is 105 mg/kg/day (Highest Dose Tested); for rabbit (41336301), the maternal NOAEL is 6 mg/kg/day and the developmental NOAEL is 8 mg/kg/day]. The multi-generation reproduction study (MRID 41352401) also reveals less severe toxicity with parental/offspring NOAEL's (4/20 mg/kg) based upon body weight loss only.

A battery of mutagenicity studies adequately demonstrates the lack of mutagenic effects exerted by this chemical. There is, however, a carcinogenicity concern associated with Propargite and it has been classified as a B2 carcinogen (CARC July 23, 1992) based upon the development of tumors in the jejunum of Sprague-Dawley rats at 400 and 800 ppm dose levels (no carcinogenicity in CD-1 mouse or Wistar rats); a revised Q<sub>1</sub>\* of 1.71 X 10<sup>-1</sup> (mg/kg/day)<sup>-1</sup> was established. The most prevalent clinical signs associated with this chemical are weight loss and GI (stomach and jejunum) perturbations.

Six metabolites have been identified, one of which appears only in female rat urine (the list of metabolites and their structures are attached). The major routes of excretion are the urinary, fecal, and biliary routes. Metabolite 1 (1-[4-(2,x-dihydroxycyclohexoxy) phenyl]-2,2-dimethyl acetic acid) is the most prevalent metabolite in the urine of male rats, while Metabolite 3 (1-[4-(1,1-dimethyl-2-hydroxyethyl)phenoxy]-2,4,5-cyclohexanetriol) is the most prevalent in the urine of female rats. Metabolite 6 is only found in female urine (1-[4-(2,4,5-trihydroxycyclohexoxy) phenyl]-2,2-dimethyl acetic acid). The kidney and liver are the organs which retained the most metabolite at a rate of ≤1.5 % of the administered dose in rat, rabbit and monkey. There were no qualitative differences found in the formation of metabolites in mouse versus rat. Pharmacokinetic studies revealed that propargite is absorbed thru the GI tract 5-7 times faster in

mice than rat . Mice also eliminated the material twice as fast as rats.

**TABLE 1: TOXICITY PROFILE FOR PROPARGITE TECHNICAL.**

Guideline No.	Study Type	MRID No.	Required	Satisfied
870.1100	Acute Oral Toxicity-Rat	41386301 43668401 43668201	Yes	Yes
870.1200	Acute Dermal Toxicity-Rat	43668402 43668202	Yes	Yes
870.1300	Acute Inhalation Toxicity-Rat	43668403 43668203	Yes	Yes
870.2400	Acute Eye Irritation-Rabbit		Yes	Yes
870.2500	Acute Dermal Irritation-Rabbit		Yes	Yes
870.2600	Dermal Sensitization-Guinea Pig		Yes	Yes
870.3200	21-Day Dermal Toxicity-Rabbit	41284101	Yes	Yes
870.6200	Acute Neurotoxicity-Rat		NA	
870.6200	Subchronic Oral Neurotoxicity-Rat		NA	
870.6100	Acute Delayed Neurotoxicity- Hen		NA	
870.6100	90-Day Delayed Neurotoxicity-Hen		NA	
870.4300	Chronic Feeding/ Carcinogenicity-Monkeys		No	Yes
870.3465	21-Day Inhalation-Rat		Yes	Yes
870.3150	Subchronic Toxicity/Dog		Yes	Yes
870.4100	Chronic Toxicity/Dog	41751401	Yes	Yes
870.4200	Carcinogenicity/Mice	00130942	Yes	Yes
870.4300	Combined Chronic Toxicity/ Carcinogenicity/Rat	41750901 42837201	Yes	Yes
870.3700	Developmental Toxicity/Rat	41346501	Yes	Yes
870.3700	Developmental Toxicity/Rabbit	41336301	Yes	Yes
870.3800	2-Generation Reproduction-Rat	41352401	Yes	Yes

870.5500	Salmonella typhimurium gene mutation	42815201	Yes	Yes
870.5575	Sacharomyces cerevisiae gene mutation	42885001	Yes	Yes
870.5500	Salmonella and E. coli gene mutation		Yes	Yes
870.5300	in vitro cytogenic study in mammalian cells		Yes	Yes
870.5550	Unscheduled DNA synthesis in rat hepatocytes		Yes	Yes
870.5500	Bacterial cells gene mutation		Yes	Yes
870.5500	Bacterial cells gene mutation		Yes	Yes
870.5900	Sister Chromatid exchange	40384603 43502202	Yes	Yes
870.5900	sister chromatid exchange in Chinese hamster ovary cells	40384602	Yes	Yes
	Clastogenicity in human lymphocytes	40982503 40982504		
870.5500	Bacterial DNA damage/repair		Yes	Yes
870.7485	Metabolism Study- Rat	43502201 41813202 41168501 41712101 41386301 41386302 41386303	Yes	Yes
Other: Special Cell Proliferation in jejunum of wistar strain rats		43766801	No	Yes

NA = not applicable

**a. Acute Toxicity**

Propargite is corrosive to the skin and eyes of rabbits (Cat. I). Acute toxicity values for

propargite in experimental animals as well as Toxicity Categories are summarized in Table 2.

**Acute Toxicity of PROPARGITE**

<b>Guideline No.</b>	<b>Study Type</b>	<b>MRID #(S).</b>	<b>Results</b>	<b>Toxicity Category</b>
870.1100	Acute Oral-Rat	42857001	LD <sub>50</sub> = 2639 mg/kg for males 2947 mg/kg for females 2800 mg/kg combined	III
870.1200	Acute Dermal-Rabbit	42857002	LD <sub>50</sub> > 2000 mg/kg	III
870.1300	Acute Inhalation-Rat	42857003	LC <sub>50</sub> = 0.95 mg/L for males 0.95 mg/L for females 0.89 mg/L combined	III
870.1400	Primary Eye Irritation-Rabbit	42857004	Corrosive	I
870.1500	Primary Skin Irritation-Rabbit	42857005	Corrosive	I
870.1600	Dermal Sensitization-Guinea Pig	42857006	Sensitizer	N/A

**b. Subchronic Toxicity**

In a repeat dose dermal toxicity study (MRID 41284101), Omite (85 % a.i.) was applied undiluted to the shaved backs of 3-4 month old, 5 New Zealand White rabbits/sex/dose at dose levels of 0, 0.1, 1.0, 10.0, and 100 mg/kg/day) for 6 hours. A total of fifteen applications were made, five days per week for three weeks. The LOAEL for dermal toxicity is 0.1 mg/kg/day, based on signs of dermal reaction. The NOAEL for dermal toxicity is <0.1 mg/kg/day. The LOAEL for systemic toxicity is 100 mg/kg/day, based on increased appearance of segmented neutrophils and mild necrosis of the liver (not stated in the original DER). The NOAEL for systemic toxicity is 10.0 mg/kg/day.

**c. Neurotoxicity**

No neurotoxicity was observed in any of the studies submitted for Propargite. Acute and developmental neurotoxicity studies have not been submitted for this chemical and are not required. (GLN 870.6100 and 870.6200).

**d. Chronic Toxicity**

In a chronic toxicity/carcinogenicity study, Omite (87.2%, a.i.) was administered to 50 Sprague-Dawley Crl:CD BR rats/sex/dose (an additional 10 rats/sex/dose were sacrifice at 53 weeks) in 0.5% corn oil in the diet at dose levels of 0, 50, 80, 400 and 800 ppm (0, 2.38, 3.83, 19.24 and 38.87 mg/kg/day for males and 0, 2.95, 4.68, 23.58 and 49.36 mg/kg/day for females) for 24 months. Males displayed the greatest reduction in body weight gain at the 400 and 800 ppm dose levels during the initial weeks of the study (at 400 ppm, weeks 0-6: -9% and -30%, respectively). Females also experienced comparable body weight gain reduction at the 400 ppm dose level; however, at 800 ppm, females showed a stronger and more sustained adverse weight gain reduction than males (week 0-6: -26.3%). Changes in relative weights of brain, liver and kidney, at the 800 ppm dose level, were not associated with any histopathologic changes and may be related to body weight decreases. The LOAEL is 400 ppm (19.24 mg/kg/day) for males due to increased mortality, decreased body weight and body weight gain, as well as, decreases in total protein and calcium. The NOAEL is 80 ppm (3.83 mg/kg/day) for males. The LOAEL is 800 ppm (49.36 mg/kg/day) for females due to decreases in body weight and body weight gain. The NOAEL is 400 ppm (23.58 mg/kg/day) for females. (GLN 870.4100 and 870.4200, MRID# 41750901)

In a chronic toxicity study, Omite (88.6 % a.i.) was administered to 6 beagle dogs/sex/dose in their diet at dose levels of 0, 160, 1250, and 1875 ppm (0, 5, 38, and 44 mg/kg/day) for 1 year. At the termination of the study, only animals at the 1875 ppm (44 mg/kg/day) dose level had significant weight loss of 23.3% and 25% of controls, for males and females respectively. Platelet levels were found to increase for high dose animals compared to concurrent and historical controls. High and mid dose animals showed mild to moderate thymic involution, as well as, stomach parietal cell vacuolization and gland dilation possibly caused by the irritant properties of the compound. In addition, the high dose animals had bone marrow atrophy and acute/subacute inflammation of skeletal muscle. The LOAEL is 1250 ppm (38 mg/kg/day, based on decreased body weight gain, and red blood cell counts; increased platelet counts and thymic involution (in females), as well as, stomach parietal cell vacuolization and gland dilation. The NOAEL is 160 ppm (5 mg/kg/day). (GLN 870.4100, MRID# 41751401)

#### **e. Carcinogenicity**

In a chronic toxicity/carcinogenicity study, Omite (87.2%, a.i.) was administered to 50 Sprague-Dawley Crl:CD BR rats/sex/dose (an additional 10 rats/sex/dose were sacrifice at 53 weeks) in 0.5% corn oil in the diet at dose levels of 0, 50, 80, 400 and 800 ppm (0, 2.38, 3.83, 19.24 and 38.87 mg/kg/day for males and 0, 2.95, 4.68, 23.58 and 49.36 mg/kg/day for females) for 24 months. Mortality for males (8/50 and 20/50 at 400 and 800 ppm, respectively) and for females (7/50 at 800 ppm) appears to be related to the increased incidence of undifferentiated sarcoma in the GI tract. There were dose related increases in incidence of jejunum tumors in both sexes. The incidences were 0, 0, 0, 10 and 15 tumors (0, 0, 0, 17% and 25%) in males and 0, 1, 0, 1, and 9 tumors (0, 2%, 0, 2% and 15%) in females for the control, 50, 80, 400, and 800 ppm dose groups, respectively (60 animals per group). They were not always associated with any increase in ulceration or other signs of irritation of the stomach or jejunum.

Tumors of the jejunum were seen in males and females receiving the highest doses of 400 and 800 ppm. The dosing was considered to be adequate to assess the carcinogenic potential of propargite. The LOAEL is 400 ppm (19.24 mg/kg/day) for males due to increased mortality, decreased body weight and body weight gain, as well as, decreases in total protein and calcium. The NOAEL is 80 ppm (3.83 mg/kg/day) for males. The LOAEL is 800 ppm (38.87 mg/kg/day) for females due to decreases in body weight and body weight gain. The NOAEL is 400 ppm (23.58 mg/kg/day) for females. (GLN 870.4100 and 870.4200, MRID# 41750901)

In a second confirmatory carcinogenicity study, Omite (89.87 % a.i.) was administered to 2 groups of 60 male Charles River CD rats in epoxidized soybean oil (used as a stabilizer) at dose levels of 0 or 800 ppm (0 or 36.3 mg/kg/day) for 2 year. For interim sacrifice, 10 rats/dose were sacrificed at one year. There was decreased survival after week 78 and no clinical behavioral effects were noted. Food consumption decreased (15-20%) along with body weight gain. Treated rats, at study termination, were found to have a lower body weight than controls. Changes in absolute and relative weights of liver, kidney, brain and testes were attributed to decreased body weight since they were not accompanied by histopathological findings. No tumors were found during the interim sacrifice. The incidence of undifferentiated sarcoma in the jejunum was found to increase significantly with treatment, 0/50 for controls versus 23/47 (49%) for the 800 ppm dose group. These tumors were found to contribute to mortality at the high dose. There was no evidence of non-neoplastic lesions such as ulcerations in the jejunum or duodenum that may have contributed to the initiation of the tumors. (GLN 870.4100 and 870.4200, MRID# 42837201)

Undifferentiated sarcoma of the GI tract is a rare tumor in rats. The nearly 50% increase in the incidence of this tumor at the 800 ppm dose in the second confirmatory study is therefore of toxicologic significance. Historical control data reveal that only 1 male of 472 (in ten studies from 1984-1988) had tumors in the duodenum and none in the jejunum. Of 479 (duodenum) and 465 (jejunum) animals examined, no females had this type of tumor.

In a mouse carcinogenicity study, Omite (purity not provided) was administered to 5 groups of 60 CD-1 mice/sex in corn oil in the diet at dose levels of 0, 50, 160, 500 and 1000 ppm (0, 7, 23, 71 and 143 mg/kg/day) for 18 months. A satellite group of 15 mice/sex was dosed with either 0, 500 or 1000 ppm (0, 71 or 143 mg/kg/day) for 12 months. No compound related mortality, effects on hematologic parameters, reduction in food consumption or body weight gain were noted. Adrenal gland and uterine absolute and relative weights were found to increase (relative weights increased 33% and 46% for adrenals and uterus, respectively). These effects were not accompanied by histopathological changes and therefore, were not considered toxicologically significant. Tumors of the gastrointestinal tract were noted in all dose groups including controls. However, none of the tumors resembled undifferentiated sarcoma seen in the rat study and no dose response was evident. In conclusion, no evidence of carcinogenicity or systemic toxicity was seen at dose levels up to 1000 ppm (143 mg/kg/day). The dosing was inadequate to access the carcinogenic potential of propargite. The LOAEL for systemic toxicity is >1000 ppm (143 mg/kg/day). (GLN 870.4200, MRID# 00130942)

#### **f. Classification of Carcinogenic Potential**

**Propargite** is classified as a **B2 carcinogen** (CARC July 23, 1992) based upon the development of tumors in the jejunum of Sprague-Dawley rats at 400 and 800 ppm dose levels. It was not carcinogenic in CD-1 mice or Wistar rats. In a memo dated November 23, 1999 by Lori Brunsman, a revised  $Q_1^*$  of  $2.01 \times 10^{-1}$  (mg/kg/day)<sup>-1</sup> was established. The evaluation of cell proliferation studies (Doc. No. 011667 and MRID 44902801) provided no evidence of a direct correlation between cell proliferation and induction of jejunal tumors. In consideration of these findings, a further review to alter the use of a non-linear extrapolation approach for human cancer risk assessment and a reclassification of Propargite to a chemical with “negligible risk at anticipated levels of human exposure” was determined to be unwarranted at this time.

#### **g. Developmental Toxicity**

In rabbit and rat developmental toxicity studies, the effects of propargite in fetuses were seen at dose levels equal to or greater than doses where maternal toxicity is seen.

In a rat developmental toxicity study, Omite (85% a.i.) was administered in corn oil by gavage to Sprague-Dawley rats, 45 female per dose, at levels of 0, 6, 12, 18, 25, or 105 mg/kg/day on gestation days (GD) 6-15 of gestation. No treatment-related maternal deaths occurred in this study. No fetal effects were noted in animals sacrificed at day 20 of gestation. The maternal LOAEL is 105 mg/kg/day, based on decreased body weight, anogenital staining, and body surface staining. The maternal NOAEL is 25 mg/kg/day. The developmental NOAEL is 105 mg/kg/day (Highest Dose Tested). (GLN 870.3700, MRID# 41346501)

In a rabbit developmental toxicity study, Omite (85% a.i.) was administered in corn oil by gavage to New Zealand White rabbits, 25 female per dose, at levels of 0, 2, 4, 6, 8, or 10 mg/kg/day on gestation days (GD) 7-19. A reduction in body weight gain occurred at doses of 8 and 10 mg/kg/day during GD 7-20 (gain of 9 g and loss of 20 g, respectively, versus a gain of 114, 165 and 119 g for control, 2 and 4 mg/kg/day, respectively). Only the incidence of fused sternebrae at 10 mg/kg/day was considered to be significantly greater than that observed in concurrent and historical controls. The maternal LOAEL is 8 mg/kg/day, based on decreased body weight gain. The maternal NOAEL is 6 mg/kg/day. The developmental LOAEL is 10 mg/kg/day, based on increased incidence of fused sternebrae. The developmental NOAEL is 8 mg/kg/day. (GLN 870.3700, MRID# 41336301)

#### **h. Reproductive Toxicity**

Propargite did not cause reproductive effects in rats but produced decreased parental and pup

body weights.

In a two-generation reproduction study, Omite (87.2 % a.i.) was administered to 25 CrI:CDBR rats/sex/dose in their diet at dose levels of 0, 80, 400, and 800 ppm (0, 4, 20, and 40 mg/kg/day) for 10 weeks then mated to produce the F<sub>1</sub>a generation. They were mated a second time after a 2 week rest period to produce the F<sub>1</sub>b generation. The F<sub>1</sub>b generation were treated in a similar manner to produce the F<sub>2</sub>a and F<sub>2</sub>b generation. No compound related clinical signs or reactions were observed for either parental group. A transient decrease in body weight gain occurred for animals in the high dose and mid dose groups. Both food consumption and food efficiency were reduced at 400 and 800 ppm. Necropsy revealed no compound related effects on gross or microscopic histological findings. There were no compound related adverse effects on the reproductive performance of any group. At the high dose, there were decreases in mean pup weight at birth and during the period of lactation. The systemic LOAEL is 400 ppm (20 mg/kg/day), based on decreased parental body weight, and food consumption. The systemic NOAEL is 80 ppm (4 mg/kg/day). The offspring LOAEL is 800 ppm (40 mg/kg/day), based on reduction of pup weight during lactation. The offspring NOAEL is 400 ppm (20 mg/kg/day). The reproductive LOAEL and NOAEL are > 800 ppm (40 mg/kg/day). (GLN 870.3800, MRID# 41352401)

#### i. Mutagenicity

**Propargite was not mutagenic in both eukaryotic and prokaryotic cell systems as illustrated in the table below.**

#### Mutagenicity Profile for Propargite (097601)

Guideline #	TYPE OF STUDY SUBMITTED	MRID No(s) YEAR	Comments (NOAEL/LOAEL)	Classification
84-2	Mutagenicity / Gene Mutation	42885001/ 1993	No evidence of mutagenicity was observed at any dose level in either the presence or absence of metabolic activation. In contrast, positive controls treated with ethylmethane sulfonate (EMS) gave definitive positive results.	Acceptable/ Guideline
84-2	CHO/HGPRT mut assay (Acetone)	42815201/ 1993	No evidence of mutagenicity was observed at any dose level in either the presence or absence of metabolic activation. In contrast, positive controls treated with ethylmethane sulfonate (EMS) gave definitive positive results.	Acceptable/ Guideline
84-2	CHO/HGPRT mut assay (DMSO) Micronucleus cytogenetic Assay-mouse	43502202/ 1994	Two males were found dead on day 3 and one female died on day 1. Clinical signs included lethargy and diarrhea in mice treated with 75 and 150 mg/kg. In these dose groups, there was a decrease in erythropoiesis but no increase in micronucleated PCEs was noted. Propargite was considered negative in this mouse micronucleus assay.	Acceptable/ Guideline
84-2	Mutagenicity / Structural Chromosomal Aberr-MNT	40384603/ 1987	Propargite was found to be negative for inducing micronuclei in bone marrow polychromatic erythrocytes of mice treated with single i.p. doses at levels up to cytotoxicity (150 mg/kg).	Acceptable/ Guideline

84-2	Mutagenicity / DNA damage/repair	40384602/1987	Omite was found to be very cytotoxic at levels above 1.67 µg/ml. However it was negative for inducing unscheduled DNA "repair" synthesis (UDS) in rat hepatocyte cultures exposed to levels below 1.67 µg/ml. The positive control, 2-aminoacetofluorene, induced a significant increase in net nuclear grains.	Acceptable/ Guideline
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#### j. Metabolism

The most significant finding of these studies was that mice absorb the chemical 5-7 times more rapidly than rats from the GI tract following oral administration. Mice also eliminated the chemical twice as fast as rats according to the finding of the intravenous study. No qualitative differences in the pattern of metabolite formation found in the mouse and the rat. Most of the labeled chemical was excreted within 24 hours in the urine (42 % males and 33.2 % females) and feces (28.9 % males and 42.6 % females). Essentially all of the label was excreted within 96 hours. There appears to be a difference in the absorption/ excretion of the metabolites with a greater amount being excreted in urine in males and in feces in females. In mice, the labeled material is more extensively metabolized. More polar metabolites and more of the metabolite, propargite glycol ether, was produced, however, the same metabolites were found in both mouse and rat feces. A metabolite (1-[4-(2,4,5-trihydroxycyclohexoxy) phenyl]-2,2-dimethyl acetic acid) was identified in female rat urine. This metabolite is apparently not found in male rat urine. Three polar metabolites were also identified at levels of 1.4 and 39.2 %: **metabolite 1**: 1-[4-(2,x-dihydroxycyclohexoxy) phenyl]-2,2-dimethyl acetic acid; **metabolite 3**: 1-[4-(1,1-dimethyl-2-hydroxyethyl)phenoxy]-2,4,5-cyclohexanetriol; and **metabolite 5**: 1-[4-(1,1-dimethyl-2-hydroxyethyl)phenoxy]-2,x-cyclohexanediol. Males were found to excrete more of metabolite 1 and 5 while females excreted more of metabolite 3 and did not form metabolite 5. **Omite glycol ether** (1-[4-(1,1-dimethylethyl)phenoxy]-2-cyclohexanol) (<5.2%) was also identified (probably a contaminant during the purification of Omite). Only 1% of the label remained in the carcass after 7 days. The liver, kidney and GI tract had the highest levels of radioactivity retained at levels of 0.1- 0.2 %. The identification and quantification of metabolites was presented in other studies (GLN 870.7485, MRID # 43502201, 41168501, 41386301,41386302, 41386303, 41813202, 41712101).

#### k. Dermal Absorption

A 14% dermal absorption factor was selected based on the highest absorption/elimination noted in either of the studies cited below. This percentage is deemed valid since it corresponds to the amount of Propargite which was actually detected in the excretions of animals.

In a dermal absorption study (MRID 40982504), Omite (89.87 % a.i.) was applied to lightly shaved backs (10 cm<sup>2</sup>) of 20 male Sprague-Dawley rats at dose levels of 0.05 mg/kg for 0, 2, 4, 8 and 24 hours. Dermal absorption of propargite for OMITE 6E formulation was <0.1% for exposures of 2 and 4 hours. Exposures of 8 and 24 hours washed and carried to 120 hours showed absorptions of 4.3 and 8.2%, respectively. A transient but significant increase in dermal absorption (wash in effect) was observed directly after the 8 and 24 hour washes. This effect may be due to the irritant properties of this chemical.

In a second dermal absorption study (MRID 40982503), Omite (89.87 % a.i.) was applied to lightly shaved backs (10 cm<sup>2</sup>) of 5 groups of 4 Sprague-Dawley rats at dose levels of 0.05, 0.5 and 5 mg/kg/day for 0, 2, 4, 8 and 24 hours. A transient but significant increase in dermal absorption (wash in effect) was again observed directly after the 8 and 24 hour washes at all doses tested. This effect may be due to the irritant properties of this chemical. There is no significant difference in the total percent absorbed with the 8 or 24 hour exposure (14.5% and 14.3% excreted, respectively).

## **l. Reference Dose**

The Health Effects Division RfD/Peer Review Committee met on June 3, 1999 and concluded, based on the available data, that propargite was not associated with any significant reproductive and/or developmental toxicity. A chronic RfD of 0.08 mg/kg/day was established based on the results of a developmental toxicity study in rabbits (MRID # 41336301) in which the LOAEL was 10 mg/kg/day. An uncertainty factor of 100 was used to account for inter-species extrapolation and intra-species variability. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to propargite as required by the Food Quality Protection Act (FQPA) of 1996. The Committee concluded that the FQPA 10 X factor should be removed.

## **m. Other Toxicological Endpoints for Risk Assessment**

On June 3, 1999, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **PROPARGITE**, established a Reference Dose (RfD) and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. HIARC re-assessed the Reference Dose (RfD) established in 1994, as well as the toxicological endpoints selected for acute dietary and occupational/residential exposure risk assessments, based solely on **animal toxicity studies**. **The June HIARC report supersedes all other reports (RfD, TES, HIARC, etc) for propargite.** (HED Doc. No. ). Table 3 provides a summary of Toxicology Endpoint Selection based on this report.

**Table 3. The doses and toxicological endpoints selected and Margins of Exposures for various exposure scenarios**

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY TYPE/ MRID
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Acute Dietary- females 13-50	NOAEL= 8  UF = 100	Increased incidence of fused sternebrae.	Developmental Toxicity in Rabbits 41336301
Acute Dietary- general population	NOAEL= N/A  UF = N/A	No relevant single exposure endpoint was identified.	N/A
	Acute RfD (females 13-50) = 0.08 mg/kg/day      Acute RfD (Gen. Pop.) = N/A		
Chronic Dietary	NOAEL = 4  UF = 100	Decreased body weight / body weight gain and increased mortality.	Chronic Feeding and Carcinogenicity in Rats 41750901
		Chronic RfD = 0.04 mg/kg/day	
Cancer Risk	Q <sub>1</sub> * = 2.01 X 10 <sup>-1</sup> (mg/kg/day) <sup>-1</sup>		
Short-Term <sup>1</sup> (Dermal)	NOAEL= 6	maternal systemic LOAEL based on decreased body weight	Developmental Toxicity in Rabbits 41336301
Intermediate-Term <sup>1</sup> (Dermal)	NOAEL= 4	parental LOAEL based on reduction in body weight	Reproductive Toxicity in Rats 41352401
Long-Term <sup>1</sup> (Dermal)	NOAEL= 4	Decreased body weight / body weight gain and increased mortality.	Chronic Feeding and Carcinogenicity in Rats 41750901
Short Term <sup>2</sup> (Inhalation)	LOAEL= 0.31mg/L or 49.6 mg/kg	LOAEL of 0.31 based on increased mortality	Acute Inhalation 42857003
Intermediate Term <sup>2</sup> (Inhalation)			
Long Term <sup>2</sup> (Inhalation)			

<sup>1</sup> A 14% dermal absorption factor will be used for risk assessment and an MOE of 100.

<sup>2</sup> An MOE of 1000 was selected, including a 10X factor due to the severity of the effects at the lowest dose tested.

On January 23, 1992, the CPDRC determined that based on the evidence presented, propargite was classified a Group B2, “likely human” carcinogen. It was concluded that administration of propargite was associated with the appearance of extremely rare jejunal tumors in male and female rats. In a carcinogenicity study in Sprague-Dawley rats, there was an increase in the incidence of undifferentiated sarcoma of the jejunum in males and females receiving 800 ppm propargite when these groups were compared to concurrent and historical controls. A  $Q_1^*$  (mg/kg/day)<sup>-1</sup> of propargite was calculated as  $2.01 \times 10^{-1}$  as documented in a memo by Lori Brunsman dated November 23, 1999 (Doc# 013867).

On August 31, 1995, new data attempting to demonstrate a mode of action (ie. cell proliferation) for the induction of tumors of the jejunum was considered (Doc. No. 011667). On September 1, 1999, additional data (MRID 44902801), voluntarily submitted by the registrant on the cause/effect relationship between cell proliferation and induction of jejunal tumors since the 1995 meeting, was evaluated. On both occasions, it was concluded that there was insufficient evidence

to warrant a re-evaluation of the classification of Propargite or the method of quantification of human cancer risk reassessment.

### **Other Toxicological Considerations**

The published literature indicates that propargite is a dermal irritant. Exposure to propargite by field workers has resulted in outbreaks of dermatitis and conjunctivitis.

### **FQPA Considerations**

The FQPA Safety Factor Committee met on August 9, 1999 to evaluate hazard and exposure data for propargite and recommend application of the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to propargite. Based on the lack of increased susceptibility following *in utero* exposure to rats and rabbits and pre/post natal exposure to rats and the adequacy of the database, the FQPA committee recommended removal of the additional 10X factor.

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